REMARKS

Claims 1-20 are pending in this application. The species under examination are:

- Claim 4: mesenchymal stem cells
- Claim 6: CD90
- Claim 7: cardiomyocytes

Further consideration and allowance of the application is respectfully requested.

Claim amendments:

Certain claims are herein amended. No new matter is introduced into the specification. Reference to "regenerative medicine" may be found throughout the specification: for example, on page 4, line 38; page 18, lines 24-30. Reference to treating both human and non-human "subjects" may be found in claim 8 as originally presented, and throughout the section from page 15, line 28 to page 19, line 3.

No substantial new limitation is added to the claims. Accordingly, coverage is maintained for all equivalents of the claimed subject matter for which applicant was previously entitled.

Request for rejoinder:

Applicant hereby renews the request for rejoinder made previously (May 7, 2003), in view of the fact that the claims stand rejected only under 35 USC § 112. No prior art has been identified that anticipates claim 1, which links each of the groups. The first cell population indicated in claim 1 links the cell types of claim 4 and the markers of claim 6. The second cell population in claim 1 links the cell types of claim 7.

MPEP § 803 indicates that a restriction requirement can only be imposed when examination of all the claims would impose a serious burden — regardless of whether the species are patentably distinct. 37 CFR § 1.141 allows applicant to present a reasonable number of species in a single application. Since claims 4, 6, and 7 each recite a reasonable number of species for each of the categories, and since no prior art has been identified, it would not impose a serious burden on the Office to examine all of the species together.

Accordingly, rejoinder and examination of all species in claims 4, 6, and 7 is appropriate. Applicant urges the Examiner to rejoin the species now, to expedite the further prosecution of this application.

Rejection under 35 USC § 112:

Claims 1-20 are still stand rejected under § 112 ¶ 1 as not being enabled by the specification to make and/or use the invention. The Office Action refers generally to the breadth of the claims, the state of the art, and the amount of guidance in the specification. The Office's position is still that the specification fails to meet the enablement requirements of § 112 ¶ 1 essentially because the specification does not include a working example of the invention. Without a working example, the Office maintains that the science standing behind this invention is too unpredictable to be enabled by the specification as filed.

Applicant respectfully disagrees. As explained previously, the case law clearly indicates that a patent applicant need not provide a working example for an invention to be enabled by the specification.

Nevertheless, previous submissions during the prosecution of this application have provided experimental evidence for the following:

1. Cardiomyocytes are a viable therapy for heart disease in human patients;
2. hPS cells and their derivatives have the properties needed in mixed lymphocyte reactions done in tissue culture to act as tolerizing cells;
3. Mesenchymal cells obtained from other sources that have the same histocompatibility type as an allograft improve survival of the allograft;
4. Cardiomyocytes can be made from hPS cells in the manner indicated in the specification
5. Cardiomyocytes *made from hPS cells* are *suitable for transplantation* in preclinical animal models; and
6. Mesenchymal stem cells *made from hPS cells* have the ability to inhibit a third-party mixed lymphocyte, demonstrating that they have *toleragenic properties that can be used for improving allograft survival* according to this invention.

The most recent Office Action refers to the Advisory Action of July 28, 2004, as indicating why this evidence has not been persuasive.

The Advisory Action questions whether cardiomyocytes and mesenchymal cells made according to the invention will have the characteristics needed to induce immunotolerance according to this application. In response, applicant hereby provides further information as to the cardiomyocytes and mesenchymal cells. New evidence from the literature is also provided that confirms the viability of the claimed invention.

Properties of ES-derived cardiomyocytes

The Advisory Action questions whether the procedures given in the specification of this application are adequate to make cardiomyocytes for use with the claimed immunotolerization strategy. Specifically, the Advisory Action suggests that some of the refinements indicated in the article by Xu et al. (Circ Res. 91(6):501-8, 2002) but not found in the present specification are critical to the functioning of the cells.

Applicant respectfully reminds the Examiner that there is no requirement to place in the specification aspects of a method that can be determined by routine experimentation, *or that is known in the art through other published information*[1]. Indeed, the immunotolerance system of this invention can be practiced to improve graft acceptance of *any* tissue type. Partly for this reason, the author of this application felt it was unnecessary to provide an exhaustive treatise on applicant's current procedures for making one particular cell type. The user of this invention may already have a cell population they wished to engraft into a recipient, and need only understand the tolerance strategy outlined in the disclosure in order to practice the invention with respect to the cell population already in their possession.

Furthermore, full methods for making cardiomyocytes in the manner of Xu et al. had already been disclosed in considerable detail at the time of filing of the present application. USSN 60/305,087, filed July 12, 2001; and USSN 60/322,695, filed September 10, 2001, were both on file before the filing date of this application, which was November 21, 2001. The 60/305,087 and 60/322,695 applications are priority documents for U.S. utility application 10/193,884, entitled "Cardiomyocyte Precursors from Human Embryonic Stem Cells", which is separately being prosecuted for protection of the hES-derived cardiomyocytes themselves. Since methods for making cardiomyocytes were already disclosed, it would be redundant and unnecessary to include the same information in the present application. The information presented on the bottom paragraph of page 11 of this application provides a summary of some of the features of a particular method, which will inspire the reader to fill in further details from what is already available to the public, including but not limited to USSN 60/305,087 and 60/322,695. A copy of USSN 60/322,695 is included in a new Information Disclosure Statement being filed contemporaneously with this Amendment.

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[1] A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

Accompanying this Amendment is a further Declaration by Joseph Gold, head of the cardiomyocyte project at Geron Corporation. Dr. Gold explains that a cardiomyocyte obtained using 5-azacytodine as described in this patent application has the same markers and functional characteristics as the cells used in the animal model experiments described in his earlier Declaration. Dr. Gold further explains that the protocol continues to undergo refinement — not to produce a different type of cardiomyocyte, but to improve efficiency of the process, which has the benefit of lowering the cost of producing the cells. The potentially higher cost of producing cells according to previous methods cannot be used as a basis for asserting that the specification was not enabling.

Properties of ES-derived mesenchymal cells

The Advisory Action also questions whether the specification is enabling for the making of mesenchymal cells having toleragenic properties.

First, the Advisory Action refers to a passage in the specification which refers to cells with a cobblestone-like appearance. The reader will understand that this is meant to describe hematopoietic cells, another species of toleragenic cells not currently under examination.

Mesenchymal cells is referred to at several places in the specification as an alternative species of toleragenic cells. The skilled reader will know that mesenchymal cells have a fibroblast-like appearance, and thus making mesenchymal cells from hES cells involves selection of cells having fibroblast-like morphology.

The new IDS includes PCT publication WO 01/51616 (published July 19, 2001), which discloses the making of the HEF1 line in Example 13. It shows the line was produced in exactly the way referred to here: hES cells were allowed to differentiate non-specifically in bulk culture, and then a population of cells having the morphological features of fibroblasts was obtained through further passaging. Subsequent studies revealed that these cells had phenotypic markers characteristic of mesenchymal cells, and also shared with mesenchymal cells the ability to make progeny of the osteoblast lineage. See Xu et al., Stem Cells 22(6):972-80, 2004 (included in the new IDS).

The Advisory Action also indicates concern that the HEF1 cell was telomerized, and says "there is no evidence indicating that the parental cell line of HEF1 would behave or share the same properties . . .". The Examiner is respectfully reminded that the burden is on the Office to indicate why the telomerized cells *would not* retain the property of the parental cells if he wishes to raise this as a concern. In fact, it is well established that transfecting a cell with telomerase reverse transcriptase restores telomere length and increases replicative capacity of the cell, but does not otherwise affect cell function (C. Harley, Oncogene 21(4):494-502, 2002). There is no evidence or rationale

suggesting that telomerizing the HEF1 cells imbued them with properties relevant to toleragenicity that were different from any other mesenchymal cells made from hES cells by standard procedures.

As of the filing date of the present application, there had already been a fill disclosure of detailed methods for making mesenchymal cells from hES cells. USSN 60/303,732 has a filing date of July 6, 2001, and is the priority application for U.S. utility application 10/189,276, entitled "Mesenchymal Cells Derived from Human Embryonic Stem Cells". A copy of the 60/303,732 application is included in the new IDS. As already explained, it is redundant and unnecessary to include the detailed text of previous disclosures in the text of the present specification, because such information is already available to the public.

Further experimental evidence for the efficacy of this invention

Included in the new IDS being filed contemporaneously with this Amendment are two recent scientific publications that provide additional evidence in support of the invention claimed here.

The first paper is by Sasaki et al., Transplantation 79(1):32-37, 2005. It shows how ES-derived cells can be used to generate microchimerism. The ES cells used were from cynomolgus macaque monkeys, which model human ES cells in all important respects (U.S. Patents 5,843,780 and 6,200,806). They were differentiated in a mixture of cytokines, and then administered to sheep by injection into the liver. As a result, donor cell-derived colony forming units (CFUs) were found in bone marrow 3-5 months later, similar to what is observed using human cord blood CD34+ve cells. Note that this model is more rigorous than the situation that would occur in human clinical use. Here the recipient animal has to be made tolerant and chimeric to cells bearing xenoantigens (i.e., substantial differences in all protein sequences including histocompatibility antigens across the species barrier from sheep to monkey), whereas human clinical use requires the recipient patient to be made tolerant only to cells bearing alloantigens (i.e., small HLA allotype differences and not much else).

The second paper is by Colson et al., J. Immunol. 173:5827-5834, 2004. It show that inducing tolerance by establishing chimerism improves engraftment of cardiac grafts. Xenogeneic chimerism was established in mice using rat bone marrow cells. The animals were then subject to complete heart replacement with mouse adult heart or xenogeneic rat newborn heart. Inducing chimerism promoted engraftment in an allotype-specific manner, promoting acceptance of matched rat heart tissue to a level comparable to autologous mouse tissue, and superior to either unmatched rat or unmatched mouse tissue (Figure 5; Table II).

Taken together, these results show that ES-derived cells successfully create chimerism in vivo, and this in turn promotes tissue-specific tolerance which improves engraftment of heart tissue in an allotype-specific fashion. Thus, if the same hES cell line is made into toleragenic cells and cardiomyocytes, the first cell population could be used to promote engraftment of the second cell population in the same fashion — in accordance with the claimed invention.

Withdrawal of the enablement rejection is respectfully requested.

Request for Allowance or Non-final Office Action

Applicant respectfully requests that all outstanding objections and rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

However, in the event the Office determines that there are other matters to be addressed before allowance of the application, it is requested that the next Office Action be non-final. By way of this Amendment and the accompanying remarks and information, applicant has made a deliberate effort to advance prosecution of the application. The RCE filed herewith provides the Office with the resources for a further full round of examination. Applicants deserve the opportunity to respond to any further issues raised without again being subject to the constraints of after-final prosecution.

Fees

Enclosed with this Amendment is authorization to charge the Deposit Account for the RCE and the extension of time.

Should the Patent Office determine that a further extension of time or any other relief is required for further consideration of this application, applicant hereby petitions for such relief, and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,

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